Remarks/Arguments

Claims 8-9 and 11-30 are canceled. Claims 1-4 and 31-35 are amended. Support for the amendments can be found, e.g., at page 25, line 10 – page 30, line 17 of the specification. No new matter is introduced.

Claims 1-7, 10, and 31-35 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

CLAIM REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH

Claims 1-7, 10, and 34-35 stand rejected for lack of enablement. More specifically, the Examiner stated:

> While being enabled for a method for melanoma prognosis comprising isolating nucleic acid from sentinel lymph node samples and blood samples obtained from a first melanoma patient and amplifying mRNA transcripts encoded by GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase genes from said nucleic acid, wherein a higher level of mRNA transcripts encoded by GalNAcT, PAX3, MART-1, MAGE-A3, and Tyrosinase genes in nucleic acid from sentinel lymph node samples and blood samples obtained from a first melanoma patient, as compared [to] the level of mRNA transcripts encoded by GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase genes in nucleic acid from sentinel lymph node samples or blood samples from a second patient with melanoma indicates that said first melanoma patient has an increased probability of metastatic melanoma recurrence, a decreased probability of metastatic-melanoma free survival, and a decrease in overall survival as compared to said second melanoma patient, and wherein a lower level of mRNA transcripts encoded by GalNAcT, PAX3, MART-1, MAGE-A3, and Tyrosinase genes in nucleic acid from sentinel lymph node samples and blood samples obtained from a first melanoma patient, as compared [to] the level of mRNA transcripts encoded by GalNAcT, PAX3, MART-1, MAGE-3A, and tyrosinase genes in nucleic acid from sentinel lymph node samples or blood samples from a second patient with melanoma indicates that said first melanoma patient has a decreased probability of metastatic melanoma recurrence, and an increased probability of metastatic-melanoma free survival, and an increase in overall survival as

compared to said second melanoma patient, the specification is NOT enabling for a method of melanoma prognosis comprising isolating nucleic acids from just any sample (including NSLN samples) obtained from a melanoma patient and amplifying just any type of nucleic acid targets from GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase, wherein an increase in expression of said targets, as compared to expression of said targets in just any control, is indicative in just any way of an increase in metastatic melanoma recurrence, a decrease in metastatic-melanoma free survival, and a decrease in patient survival as compared to just anyone else *and a decrease in the levels of the nucleic acid targets is indicative in just any way of a decrease in melanoma recurrence, an increase in disease-free survival, or an increase in overall survival as compared to just anyone else.* (the "Office Action," page 9, line 2 – page 10, line 10; emphases original)

Although Applicants do not concede the Examiner's position, for the sole purpose of moving this application forward, Applicants have amended claim 1 as follows in view of the Examiner's statement cited above:

1. A method for melanoma prognosis, comprising:

(a) isolating nucleic acid from a sentinel lymph node (SLN) sample obtained from a first melanoma patient;

(b) amplifying mRNA transcripts encoded by a panel of marker genes from the nucleic acid from the SLN sample obtained from the first melanoma patient, wherein the panel comprises GalNAcT, PAX3, or both;

(c) detecting the levels of the mRNA transcripts encoded by the panel of marker genes in the nucleic acid from the SLN sample obtained from the first melanoma patient; and

(d) predicting metastatic melanoma recurrence, metastatic melanoma-free survival, overall survival, or a combination thereof, for the first melanoma patient, wherein, as compared to the levels of mRNA transcripts encoded by the panel of marker genes in nucleic acid from an SLN sample obtained from a second melanoma patient, higher levels of the mRNA transcripts encoded by the panel of marker genes in the nucleic acid from the SLN sample obtained from the first melanoma patient indicate that the first melanoma patient has an increased probability of metastatic melanoma recurrence, a decreased probability of metastatic melanoma-free survival, or a decreased probability of overall survival, and lower levels of the mRNA transcripts encoded by the panel of marker genes in the nucleic acid

from the SLN sample obtained from the first melanoma patient indicate that the first melanoma patient has a decreased probability of metastatic melanoma recurrence, an increased probability of metastatic melanoma-free survival, or an increased probability of overall survival.

Since amended claim 1 recites SLN samples (not just any samples), mRNA transcripts (not just any type of nucleic acid targets), a second melanoma patient (not just any control), an increased / decreased probability of metastatic melanoma recurrence, a decreased / increased probability of metastatic melanoma-free survival, or a decreased / increased probability of overall survival compared to that for a second melanoma patient (not in just any way as compared to just anyone else), it is fully supported by the specification (see, e.g., page 25, line 10 – page 30, line 17 of the specification).

Claim 34 is amended likewise. Amended claim 34 is fully supported by the specification and Koyanagi et al. (2005) J Clin Oncol 23(31):8057-64, the abstract of which was submitted as "Exhibit A" with Applicants' response to the office action dated March 24, 2006.

Claim 35 is also similarly amended. Amended claim 35 is fully supported by the specification and Dr. Hoon's Declaration dated December 15, 2006 and submitted with Applicants' response to the office action dated September 15, 2006. More specifically, the invention is directed in part to detection of micro metastasis in cancerous lymph nodes by using multimarker real-time reverse transcriptase polymerase chain reaction (qRT-PCR) (see, e.g., page 2, lines 12-14 of the specification). Lymph nodes include both sentinel lymph nodes (SLN) and non-sentinel lymph nodes (NSLN). SLN is the first node that receives metastatic melanoma cells and reflects the metastatic status of the entire lymphatic basin including NSLN. See, e.g., page 3, lines 15-24 of the specification. Therefore, NSLN can be used in the methods of the invention just like SLN. This is confirmed

by the results provided in Dr. Hoon's Declaration dated December 15, 2006. Among 11 NSLN-positive (i.e., at least one melanoma marker detected by qRT-PCR) patients, 8 were found to be SLN-positive, while only 3 were found to be SLN-negative (Dr. Hoon's Declaration dated December 15, 2006, page 3, lines 3-5). Further, consistent with the finding that 53% SLN-positive melanoma patients had disease reoccurrence, melanoma reoccurred in 73% of NSLN-positive patients (see, e.g., page 28, lines 7-9 of the specification and Dr. Hoon's Declaration dated December 15, 2006, page 3, lines 5-6). In this connection, Applicants respectfully point out that "[t]he law does not require a specification to be a blueprint in order to satisfy the enablement requirement," and that one need not necessarily disclose how to make each and every embodiment encompassed by a claim. See, e.g., Staehlin v. Secher, 24 U.S.P.Q. 2d 1513, 1516 (Bd. Pat. App. & Int. 1992). Claim 35 is sufficiently enabled by the specification and Dr. Hoon's Declaration dated December 15, 2006.

In light of the foregoing, Applicants submit that claims 1 and 34-35, as amended, are fully enabled. Claims 2-7 and 10, dependent directly or indirectly from claim 1, also satisfy the enablement requirement. Withdrawal of the rejections is thus respectfully requested.

CLAIM REJECTIONS UNDER 35 USC § 103(a)

Claims 31-33 stand rejected as being unpatentable over Palmieri et al. (Journal of Clinical Oncology 19(5):1437-1443; "Palmieri") in view of Scholl et al. (Cancer Research 61:823-826; "Scholl") and Kuo (Clinical Cancer Research 4:411-418; "Kuo"). Applicants respectfully traverse.

Claim 31 is directed to a method for detecting the expression of a panel of marker genes including GalNAcT or PAX3 in an SLN sample from a melanoma patient and histopathologically negative for melanoma cells. In contrast, Palmieri

discloses detection of Tyrosinase and MART-1 in histopathologically negative SLN samples obtained from melanoma patients (see page 1437, left column, 1st paragraph, lines 7-12 and 2nd paragraph, lines 3-5). Scholl discloses detection of PAX3 in cultured primary melanomas and their corresponding tissue sections (see page 823, left column, Abstract, lines 5-11 and right column, last paragraph, lines 4-6). Kuo discloses detection of GalNAcT in melanoma cell lines, primary melanoma biopsies, histopathologically positive tumor-draining lymph node (TDLN) metastases, distal organ metastases, and blood (see page 413, right column, Table 1 and 1st paragraph following Table 1, lines 14-15; page 414, left column, Table 2). None of the three references discloses detection of GalNAcT or PAX3 in histopathologically negative SLN samples. The Examiner asserted that there would be a reasonable expectation of success in detecting GalNAcT or PAX3 in histopathologically negative SLN samples because Palmieri teaches detection of two other markers and detection of genes is well known and conventional in the art. Applicants respectfully submit that the Examiner's assertion has no basis in the cited art.

More specifically, Palmieri, Scholl, and Kuo do not indicate whatsoever that GalNAcT or PAX3 would share the same expression pattern as Tyrosinase and MART-1 simply because they are all melanoma markers. Furthermore, it is well known in the art that not all genes are detectable in all types of samples and that a melanoma marker detected in one type of samples from melanoma patients is not necessarily detectable in another type of samples from melanoma patients. For example, Kuo demonstrates that, while GalNAcT is detected in blood samples from AJCC stage II, III, or IV melanoma patients, it is not detected in blood samples from AJCC stage I melanoma patients (see page 415, left column, Table 3). Likewise, the detection of PAX3 in cultured primary melanomas and their corresponding tissue sections and the detection of GalNAcT in melanoma cell lines,

primary melanoma biopsies, histopathologically positive tumor-draining lymph node (TDLN) metastases, distal organ metastases, and blood do not indicate at all that GalNAcT and PAX3 would be detectable in histopathologically negative SLN samples from melanoma patients. Therefore, even if one skilled in the art would have been motivated to combine Palmieri with Scholl and Kuo, there would have been no reasonable expectation of success in detecting PAX3 or GalNacT in histopathologically negative SLN samples from melanoma patients.

In conclusion, claim 31 is patentable over the cited art. Claims 32-33, dependant directly or indirectly from claim 31, are also patentable over the cited art for at least the same reasons. The rejections should be withdrawn.

CLAIM REJECTIONS UNDER 35 USC § 112, SECOND PARAGRAPH

Claims 1-7, 10, and 31-35 are rejected for being indefinite. Although Applicants disagree with the Examiner, to expedite the prosecution of this application, Applicants have amended claims 1, 31, and 34-35 to overcome this rejection. Claim 1 is used as an example in the following discussion.

In claim 1, "nucleic acid targets from a panel of marker genes" has been replaced with "mRNA transcripts encoded by a panel of marker genes." The predictably increased / decreased melanoma recurrence, disease-free survival, or overall survival has also been clarified. The levels of the mRNA transcripts encoded by the panel of marker genes in the nucleic acid from the SLN sample obtained from the first melanoma patient are compared with the levels of mRNA transcripts encoded by the panel of marker genes in nucleic acid from an SLN sample obtained from a second melanoma patient. If the levels of the mRNA transcripts encoded by the panel of marker genes in the nucleic acid from the SLN sample obtained from the first melanoma patient are higher than the levels of the mRNA transcripts encoded by the panel of marker genes in the nucleic acid from the SLN sample

obtained from the second melanoma patient, the first melanoma patient has an increased probability of metastatic melanoma recurrence, a decreased probability of metastatic melanoma-free survival, or a decreased probability of overall survival. If the levels of the mRNA transcripts encoded by the panel of marker genes in the nucleic acid from the SLN sample obtained from the first melanoma patient are lower than the levels of the mRNA transcripts encoded by the panel of marker genes in the nucleic acid from the SLN sample obtained from the second melanoma patient, the first melanoma patient has a decreased probability of metastatic melanoma recurrence, an increased probability of metastatic melanoma-free survival, or an increased probability of overall survival. Finally, amended claim 1 clearly indicates that mRNA transcripts encoded by a panel of marker genes are amplified from the nucleic acid from the SLN sample obtained from the first melanoma patient.

In light of the foregoing, Applicants submit that amended claims 1, 31, and 34-35 are definite because they particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claims 2-7 and 10, dependent directly or indirectly from claim 1, are definite for at least the same reasons. Withdrawal of the rejections is thus respectfully requested.

NEW MATTER

Claim 35 is rejected for containing new matter. Applicants respectfully traverse. As mentioned above, the specification, as filed, indicates that the invention is directed in part to detection of micro metastasis in cancerous lymph nodes by using qRT-PCR (see, e.g., page 2, lines 12-14 of the specification). The specification, as filed, further indicates that lymph nodes include both sentinel lymph nodes (SLN) and non-sentinel lymph nodes (NSLN). SLN is the first node that receives metastatic melanoma cells and reflects the metastatic status of the

entire lymphatic basin including NSLN. See, e.g., page 3, lines 15-24 of the specification. In view of such disclosure in the specification, one skilled in the art would understand that NSLN can be used in the methods of the invention just like SLN. In other words, the specification, as filed, reasonably conveys to one skilled in the art that Applicants had possession of the claimed invention at the time the application was filed. Therefore, claim 35 contains no new matter and meets the written description requirement. The rejection should be withdrawn.

DOUBLE PATENTING

Claims 1-7, 10, and 31-35 are provisionally rejected on the ground of non-statutory obviousness-type double patenting over claims 1-16 of co-pending US Patent Application No. 11/227,575. If the pending claims are found to be otherwise allowable except for this ground of rejection, Applicants will submit an appropriate terminal disclaimer. In this event, Applicants respectfully request that the Examiner telephone the undersigned who will then provide the terminal disclaimer.

CONCLUSION

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned at the Los Angeles, California telephone number (310) 785-4751 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
HOGAN & HARTSON L.L.P.

Date: July 30, 2007

By: _____

Y. Jenny Luo, Ph.D.
Registration No. 54,284
Patent Agent for Applicants

1999 Avenue of the Stars, Suite 1400
Los Angeles, California 90067
Phone: 310-785-4600
Fax: 310-785-4601